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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	AH0948Q
First Inventor or Application Identifier	SHIH, et al
Title	IMPROVED GROWTH STIMULANT COMPOSITIONS
Express Mail Label No.	EL226882657US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231**

1. [X] * Fee Transmittal Form *(e.g., PTO/SB/17)* *(Submit an original and a duplicate for fee processing)*
2. [X] Specification [Total Pages 22] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) *(35 U.S.C. 113)* [Total Sheets]
4. Oath or Declaration [Total Pages]
   - a. [ ] Newly executed (original or copy)
   - b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d)) *(for continuation/divisional with Box 16 completed)*
     - i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

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5. [ ] Microfiche Computer Program *(Appendix)*
6. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   - a. [ ] Computer Readable Copy
   - b. [ ] Paper Copy (identical to computer copy)
   - c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
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12. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
13. [ ] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application, Status still proper and desired
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17. CORRESPONDENCE ADDRESS

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PATENT CASE AH0948Q

IMPROVED GROWTH STIMULANT COMPOSITIONS

FIELD OF THE INVENTION

The invention relates generally to veterinary pharmaceutical compositions and formulations that control the release of the active compound therein to the animal. More specifically, the present invention discloses actives in a dual formulation that stimulates growth and weight gain in domestic animals.

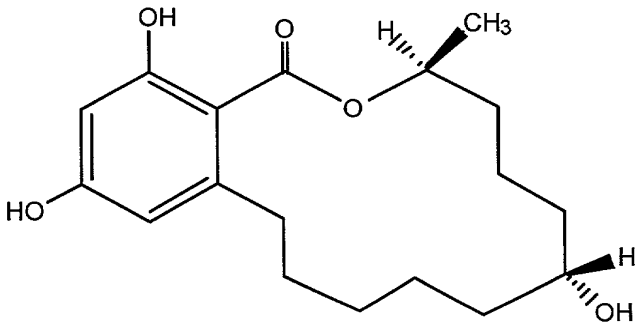
BACKGROUND OF THE INVENTION

There have been many recent advances in the veterinary sciences and veterinary pharmacology that have resulted in the growth and development of larger, healthier and heartier, bovine, porcine, ovine and equine species. Particularly with respect to the bovine, ovine and porcine groups, the need to feed the world's population through the production of meat provides the impetus to raise domestic animals that grow as quickly and as large as possible.

Anabolic agents, are widely used to promote the growth of cattle and other domestic animals and stimulated growth promotion is desirable among the cattle farmers because it maximizes both rate of weight gain and the absolute amount of weight gain per average amount of food consumed, which is termed feed efficiency. Generally, steroids are supplied to the animal in the form of a bio-degradable or non-biodegradable, implantable, time release pellet(s) which is injected under the skin using an implant device. These have been proven to be successful; however, the animals may have to be implanted 2-4 times during their growth period.

The implant devices used for the subcutaneous delivery of these steroid pellets consist of a housing in the shape of a pistol with a handle, a hollow needle for injecting the pellet into the body of the animal located at the front side of the housing, and a push-rod. The push-rod can be slid into this hollow needle and is supported in the housing so as to be displaceable longitudinally. A chamber is provided in the housing and is attached to the needle. A magazine containing the pellets is inserted and displaceable therein. A longitudinally displaceable press-back device (spring ejector) is arranged in the housing parallel to the push-rod and hollow needle in the housing. The push-rod and press-back device are moved by a driving mechanism which is similarly provided in the housing and which can be set in motion by the operating lever (trigger) fastened to the handle. This engages the driving mechanism and press-back device via a toothed segment coupled with the operating lever and a toothed wheel engaging the press-back device and push-rod. Such a device design is described, for example, in U.S. patent 5,514,101.

Zeranol (Formula I, CAS Registry Number: 26538-44-3) is an anabolic agent which has shown impressive results in the promotion



Formula I

of weight gain and growth in cattle. Zeranol, a resorcylic acid lactone derivative, has shown to be a positive influence on dynamic protein metabolism. However, during the growth and development of the cattle, current formulations containing zeranol or other such anabolic agent must be administered at least twice over the 170 day growth and development period for optimal results. Obviously, this necessitates bringing cattle in

from the fields, reinjecting the implant and transporting them out again which is a laborious and time-consuming process.

It has been determined that zeranol and other anabolic agents provide the best growth and weight gain results when administered early on and throughout the animal's growth cycle. This would require a dual immediate-release/sustained-release formulation which has been hereinbefore not possible.

United States Patent No. 5,643,595 to Lewis discloses and claims a delivery system for veterinary growth promotants consisting of a biodegradable polymeric matrix that contains a steroid growth promotant and an antibiotic. The steroid growth promotant may consist of zeranol which is formulated within sustained-release microparticles consisting of homopolymers or copolymers of lactic and/or glycolic acid. Other biodegradable polymers used in the sustained-release formulations include polycaprolactone, polydioxonene, polyorthoesters, polyanhydrides, waxes, casein and mixtures thereof.

United States Patent No. 5,427,796 also to Lewis discloses a method for increasing animal growth comprising the administration of an anabolic steroid such as zeranol in a biodegradable microparticle delivery system that releases the drug in a multiphasic manner. Drug delivery duration allegedly lasts up to 200 days. The same polymers are used in Lewis's other patents noted above and below.

United States Patent Nos. 5,419,910 and 5,288,496 to Lewis also disclose and claim a microparticulate sustained-release delivery system for promoting growth in animals. The microparticles are comprised of a biodegradable polymeric matrix such as poly-d,l-lactic acid, polyglycolic acid and the like. The microparticles separately encapsulate a steroid growth promotant and an antibiotic. Zeranol, among other anabolic steroids, is disclosed as one of the useful actives that result in increased bulk weight and growth.

United States Patent No. 4,874,612 to Deasy discloses a multi-component implant for the sustained-release, long-term delivery of pharmaceutical agents to humans and animals for the treatment of vitamin deficiencies, hormone replacement therapy, cancer therapy, infection and

the like. Preferably, the biodegradable polymers comprising the implants are used to deliver animal growth promotants which contain anabolic steroids such as zeranol as well as their combinations. The matrix used to make the implants consists of lactic acid/glycolic acid copolymers.

United States Patent No. 4,191,741 to Hudson *et al* discloses and claims polymeric implants for the long-term sustained-release of anabolic agents to ruminant animals. The steroids can be administered alone or in combination, one of which is estradiol. Zeranol is not specifically disclosed as one of these agents.

In fact, the use of biodegradable particles for the long-term, sustained-release of anabolic steroids and other pharmaceutical actives is known in the art. See for example, United States Patent Nos. 4,683,288; 4,677,191; 4,675,189; 4,542,025; 4,530,840; 4,489,055 and 4,389,330.

Unfortunately, not all of the prior art delivery systems enable zeranol to be administered in a way that maximizes the growth and weight gain potential that exists. Whereas zeranol and other anabolic agents must be administered two to four times during the growth phase of the animal, it would be most advantageous to provide a formulation that need only be administered once.

It is an object of the present invention to provide an anabolic implant formulation for increased growth and weight gain significantly greater than that achieved by animals given other steroid therapies and those given none at all. It is a further object of the present invention to provide an anabolic implant formulation that is given only once during the growth phase of the animal yet provides both immediate and sustained, long-term administration of the drug throughout the growth period for optimal growth and weight gain.

SUMMARY OF THE INVENTION

The above-noted objects and others are addressed by aspects of the present invention which provides a method and an anabolic implant formulation for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle. The inventive method comprises administering to the animal an implant composition (or implant

as is commonly called) which comprises: (i) an immediate-release formulation containing an anabolic agent, and (ii) a controlled-release formulation containing an anabolic agent with a controlled-release agent, wherein the immediate-release formulation and the controlled-release formulation cooperate to effect the desired stimulation of growth and weight gain. The immediate-release formulation and the controlled-release formulation may be simultaneously administered, or one immediately followed by the other in quick succession in whichever order the administrator chooses, to the animal. Applicants have found that the inventive method of administering a dual formulation surprisingly results in growth and weight gain in the animal much higher than when either formulation (i) or (ii) is implanted without the other.

The present invention further discloses a method of preparing the above-noted dual formulation, an anabolic implant composition comprising a dual formulation, as well as a method for stimulating growth and weight gain in animals using such compositions.

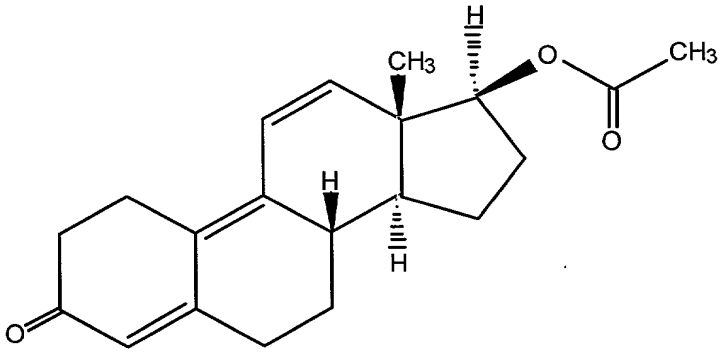
DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, this invention discloses a method for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in animals, sometimes generally referred to as cattle in this application. The method comprises administering an anabolic implant composition which is a dual formulation comprising (i) an immediate-release formulation containing an anabolic agent, and (ii) a controlled-release formulation containing an anabolic agent and a controlled-release agent. The immediate-release formulation and the controlled-release formulation cooperate in the cattle to effect the desired stimulation of growth and weight gain. Even though the dual formulation may be administered as one composition by simultaneous administration of both (i) and (ii) above in one administrating (injecting) device, or administered one formulation followed by the other in quick succession in whichever order the administrator prefers, the following description, for simplicity sake, describes the invention as a single step simultaneous administration method.

The present invention concerns a method of stimulating increased rate of growth, greater amount of growth and greater feed efficiency in food animals which comprises providing to such animals biodegradable and non-biodegradable compressed tablets loaded with an anabolic agent. The method of the present invention provides advantages over methods known in the art such as, *inter alia*, increased weight gain, a biodegradable or nonbiodegradable system, an implant system, the ability to mix tablets (pellets) containing different drugs and the ability to program the release rate (multiphasic release patterns).

In a preferred embodiment, administration of the growth promotant to food animals by the method of the invention is achieved by a single administration of the growth promotant loaded into compressed shapes such as, for example, tablets which release the active anabolic agent into the animal in a constant or pulsed manner and eliminates the need for repetitive injections. Some of the tablets contain the active anabolic agent with no controlled-release agent, while the other tablets contain the active anabolic agent with a controlled-release agent, as described later in the **Examples**. Thus, the former acts as the immediate-release formulation while the latter acts as the controlled formulation.

The anabolic agent used in the two formulations may be the same or different. Illustrative anabolic agents suitable for and useful as growth promotants in the present invention include zeranol, estradiol and its derivatives such as, for example, estradiol benzoate, trenbolone acetate (Formula II, CAS Registry Number: 10161-34-9, available from Pharmacia & Upjohn Company, Kalamazoo, Michigan), somatotrophin and its derivatives, testosterone and its derivatives such as, for example, testosterone propionate, salbutamol, progesterone, its derivatives and combinations thereof.



Formula II

In the immediate-release formulation, the anabolic agent may be used as it is or optionally formulated with minor amounts of other materials such as, for example, diluents, excipients, tabletting agents and the like that are suitable for insertion under the skin. Examples of some of these materials include lactose as a diluent, magnesium stearate as a lubricant, silica as a glidant and the like. For example, the commercially available Ralgro® is formulated with lactose. Other diluent materials include, for example, mannitol, sorbitol, sucrose, dextrose, starches, hydrolyzed starches, and the like.

In the controlled-release formulation (also referred to as sustained-release formulation in this application), generally the controlled-release agent is a polymer matrix. The polymeric matrix material must be biocompatible. The term biocompatible is defined as a polymeric material which is not toxic to an animal and is not carcinogenic. Whereas the matrix material is biodegradable, the polymeric material should degrade by bodily processes to products readily disposable by the body and should not accumulate therein. When the matrix is non-biodegradable, it is still biocompatible and may remain within the animal at the site of implantation indefinitely. Suitable examples of polymeric matrix materials useful in the present invention include poly(D,L-lactide-co-glycolide) copolymer, ethyl cellulose, methyl acrylate-methyl methacrylate copolymer, methylcellulose, hydroxyethyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethyl cellulose, and the like. As in the immediate-release formulation, the anabolic agent and the polymer matrix material in the controlled-release formulation may be optionally formulated with minor

amounts of other materials such as, for example, diluents, excipients, tabletting agents and the like, that are suitable for insertion under the skin. Examples of some of these materials include lactose as a diluent, magnesium stearate as a lubricant, silica as a glidant and the like.

The implant is generally in the shape of a cylindrical tablet. The tablet will generally have a diameter of from about 2.0 mm to 6.0 mm and a length of from about 1.0 mm to about 4.0 mm. The implants for the controlled-release are generally prepared by a procedure wherein the active anabolic agent is mixed with the poly(D,L-lactide-co-glycolide) copolymer or the ethyl cellulose together with the other optional materials and this is then compressed in the die of a tabletting press as is known in the art. Suitable illustrative procedures to make such implants with biodegradable polymer and with non-biodegradable polymer are described later in this application.

The rate of release of the anabolic agent in the controlled-release formulation can be controlled by a variety of measures. With respect to the poly(D,L-lactide-co-glycolide) copolymer, the rate of degradation of the carrier matrix can be increased by decreasing the size and consequently the molecular weight of the polymer chains. Increasing the amount of the active anabolic agent and consequently reducing the active copolymer weight ratio will increase rate of release. The incorporation of additional plasticizers and other excipients may even speed up the degradation and release. Such modifications will be obvious to those skilled in the art.

The preparation of the implants containing a biodegradable polymer such as, for example, the poly(D,L-lactide-co-glycolide) copolymer, may be achieved utilizing any number of methods known in the art. An illustrative procedure is as follows. Preferably the anabolic active is first dissolved in a suitable solvent that will also solubilize, emulsify or disperse the poly(D,L-lactide-co-glycolide) copolymer. Suitable solvents include organic solvents such as acetone, chloroform, methylene chloride, other aromatic hydrocarbons, cyclic ethers, esters, alcohols and the like and mixtures thereof. The polymer matrix material is also dissolved or dispersed in the solvent and the emulsion or solution formed thereby may be mixed into a

continuous phase. A surfactant may be added to the solution to prevent agglomeration.

The solvent is then removed, generally by the application of heat, the application of reduced pressure or both. The temperature employed is not critical but it should not be so high as to result in a degradation of either the active compound or the implant biodegradable matrix material. Once the solvent is removed, the solid dose implants may then be prepared using a standard tabletting die press as is known in the art.

Preferably, the anabolic agent useful in the formulation of the present invention is zeranol. A commercially available formulation of zeranol is Ralgro® (from Schering-Plough Corporation, Terre Haute, Indiana) which additionally contains some lactose. The zeranol content in the present formulation is in an amount of from about 50 wt.% to 95 wt.% preferably from about 55 wt.% to about 85 wt.% and most preferably from about 60 wt.% to about 80 wt.%, based on the total weight of the implant composition (including both the immediate-release part and the controlled-release part).

The poly (D,L,-lactide-co-glycolide) copolymer is incorporated in the sustained-release formulation in amounts ranging from about 1.0 wt.% to about 10 wt.% and preferably from about 1.0 wt.% to about 5.0 wt.%. If ethyl cellulose is used as the agent in place of the poly(D,L-lactide-co-glycolide) copolymer, greater amounts may be used such as from about 1.0 wt.% to 8.0 wt.% and preferably from about 2.0 wt.% to about 7.0 wt.%.

The other optional materials may be added to the formulation according to the length of drug delivery desired, but for the most part these will be added in standard amounts as is known in the art. For example, a diluent or excipient may be added in amounts of from about 20wt.% to 40 wt.%, preferably in an amount of from about 25wt.% to 40 wt.%, and typically in amounts of from about 25 wt.% to 30 wt.%. Coloring dyes for foods, drugs & cosmetics ("FD & C"), and the like may be incorporated into the formulations in amounts of from 0.1 wt.% to 2.0 wt.% as is known in the art.

Implants containing non-biodegradable polymer such as, for example, ethyl cellulose, may be prepared by procedures known in the art.

An illustrative procedure is as follows: The anabolic agent such as zeranol is mixed with a diluent such as, for example, lactose, and optionally a suitable dye in a planetary mixer. In a separate mixer, an aqueous dispersion of ethylcellulose commercially available as Aquacoat ECD-30® (available from FMC Corporation, Philadelphia, Pennsylvania) is mixed with a suitable plasticizer such as triacetin, or dibutyl sebacate, etc. The plasticized ethyl cellulose is then blended with the anabolic agent/lactose mixture and granulated. The granules are dried at a temperature of from about 50° c to 70° C until the formulation is characterized by a moisture level of from about 0.2 wt.% - 0.6 wt.% based on the total weight of the formulation. The dried granules are then sized through a sieve, such as, for example, the Fitzmill sieve or its equivalent, and then lubricated with an appropriate lubricant such as magnesium stearate and a glidant such as, for example, silicon dioxide. The granules are then compressed into pellets of the desired size and hardness.

Without being bound to any theory, it is believed that ethyl cellulose which is a pseudolatex matrix is distributed evenly throughout the wet mass. Upon drying, the matrix particles become finely blended with the active anabolic agent and the excipients. Compression in the tablet die further condenses the ingredients together.

A heating or curing step is important as this seems to fuse or coalesce the ethyl cellulose particles forming a true matrix structure about the active. This results in the active anabolic agent/excipient blend being fully entrapped by the ethyl cellulose chains.

For the immediate-release formulation, compositions such as the commercially available zeranol product, such as, for example, Ralgro®, may be used and compressed into suitable size tablets. Any optional ingredients such as, for example, dye and the like, may be mixed in before compressing into tablets.

The inventive dual formulation is prepared by taking a certain number of thus-prepared tablets containing the controlled-release formulation and a certain number of thus-prepared immediate-release formulation (including Ralgro® which is zeranol plus lactose) tablets in the

injection device. The number of each kind is determined based on the total amount of zeranol one desires to inject into the animal. For comparison purposes, the dual formulation injection may be compared with injection of either the controlled formulation tablets alone or the zeranol tablets alone such that the total amount of zeranol would still match with the total zeranol in the inventive dual formulation. The growth enhancement implant pellets are generally subcutaneously injected into the cattle, or other domesticated animal under the ear. After administration, water diffuses into the tablet from the tissue of the animal and is driven by hydration of the lactose and to a small extent by hydration of the anabolic agent. The dissolved active then diffuses out of the matrix structure and into the animal's systemic circulation. As the EXAMPLES demonstrate, Applicants found that the inventive dual formulation tablets surprisingly resulted in a higher increase of growth and weight gain in the test animals than either the controlled-release tablets alone or the zeranol tablets alone.

Another embodiment of the present invention discloses anabolic implant compositions and formulations for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle. The inventive composition is a dual release formulation which comprises: (i) an immediate-release formulation containing an anabolic agent, and (ii) a controlled-release formulation containing an anabolic agent and a controlled-release agent, wherein the immediate-release formulation and the controlled-release formulation cooperate to effect the desired stimulation of growth and weight gain. The types and examples of (i) and (ii) are described above.

A further embodiment of the present invention discloses a method of stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle, whose growth, weight gain and feed efficiency need to be improved, by administering to said cattle an anabolic implant composition which is a dual release formulation which comprises: (i) an immediate-release formulation containing an anabolic agent, and (ii) a controlled-release formulation containing an anabolic agent and a controlled-release agent, wherein the immediate-release formulation and the controlled-release formulation cooperate to effect the desired

stimulation of growth and weight gain. The types and examples of (i) and (ii) are described above.

A still further embodiment of the present invention concerns a method for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in an animal. The method comprises: preparing an immediate-release formulation comprising an anabolic agent such as, for example, the agents described above, in a shaped object suitable for loading into a device such as, for example, pellets, tablets and the like, which device is suitable for administration of said shaped object into the animal (such as, for example, the pistol described earlier); preparing a controlled-release formulation containing an anabolic agent and a controlled-release agent, in a shaped object similar to above and suitable for loading into the device in step (a), wherein said anabolic agent in step (a) and said anabolic agent in step (b) may be the same or different; loading the device with the shapely object in step (a) and the shapely object in step (b) in a ratio such that the total anabolic agent is in the 50-95 weight percent range based on the combined weight of the two formulations (i.e. the formulation in step (a) and the formulation in step (b)); and administering the shaped objects into the animal, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect the desired stimulation. Suitable controlled agents and methods for making the formulations are described above.

The following EXAMPLES are provided to more fully describe how to make and use the implants of the present invention, as well as to demonstrate the superior results attained thereby. It should be noted however that the examples are for illustrative purposes only and that minor changes or variations may be made in the amounts and/or methods that are not covered therein. It should also be noted that to the extent any such changes or variations that do not materially alter the composition or effects of the final product are deemed as falling within the spirit and scope of the present invention as later recited in the claims.

EXAMPLES

EXAMPLE 1: Comparison of Weight Gain with Zeranol as Immediate-release Formulation to a Formulation Containing Zeranol as Controlled-release Formulation: The following zeranol matrix base formulations were prepared to compare controlled-release formulations containing zeranol with Ralgro® and a placebo (an ineffective control). As stated earlier, Ralgro® is a commercially available product of zeranol and lactose.

Formulation	Composition
A	Controlled-release Formulation: zeranol/poly(D,L-lactide-co-glycolide copolymer; 50:50 wt%) (180 mg total zeranol)
B	Controlled-release Formulation: zeranol/ethyl cellulose (50:50 wt%, 180 mg total zeranol)
C	Ralgro® (36 mg zeranol)
D	Placebo: no Zeranol

The implants were prepared as follows. For formulation A, the poly (D,L-lactide-co-glycolide 50:50, 3.991 g) was placed in an Erlenmeyer flask and dissolved in 50 grams of ethyl acetate. Separately, the zeranol and lactose (26.606 g) were mixed together dry in a mortar to which the FD & C coloring dyes (0.44 g) were added. The solvent comprising D,L-lactide-co-glycolide and ethyl acetate was then added to the zeranol/dye/lactose mixture. The composition was then heated to 40-45°C. to complete dryness and granulated and sized through a 25 mesh screen. A Cab-O-Sil® silica glidant (0.665 g) was added along with magnesium stearate (1.33 g) which was added as a lubricant. The compositions were then compressed in a tabletting die to obtain solid implants (26.606 mg each implant) with a hardness of 12-20 Strong Cobb units. Formulation B was prepared in a similar manner using ethyl cellulose as the polymer matrix and Aquacoat ECD-30 instead of ethyl acetate. For formulation C, Ralgro®

was made into similar size tablets using procedures known in the art. And formulation D, the control with no zeranol was made into tablets similar to in formulation C.

The implants were administered to twenty (20) steers subcutaneously under the ear. In order to properly compare the formulations of the present invention with those of the prior art, formulation C was administered twice, once at day 0 and again at day 70, each dose containing 36 mg of zeranol. Each steer was weighed at selected time periods during its development and the average body weight for each group given a particular formulation A to D was calculated for each date and are as follows:

Table 1

Treatment	Day 0	Day 28	Day 56	Day 70	Day 84	Day 112	Day 140	Day 168	Day 182
A	339	423	483	544	562	616	693	765	803
B	337	426	492	558	568	631	701	780	806
C	339	431	506	562	578	644	716	812	838
D	342	420	473	531	536	593	645	709	742

The results show that the weight gain with either controlled-release formulation (A or B) is slightly lower than or, at best, statistically equivalent to that of the Ralgro® re-implant program of formulation C.

Example 2: Comparison of Weight Gain with Inventive Dual Formulation versus Weight Gain with Immediate Formulation alone, or with Controlled Formulation alone: The effects of implanting the dual immediate-release/controlled-release pellets of the present invention on weight and growth gain were studied and compared with zeranol (as

Ralgro®) alone, with controlled-release formulation alone and with a non-effective placebo control. That could be done by replacing certain controlled-release tablets of Example 1 with Ralgro® tablet(s). The administered dosages were as follows. The total weight administered is shown in brackets.

Formulation Composition

E Placebo control; no zeranol

F Ralgro® (36 mg zeranol; 3 pellets 12 mg each)

G Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release-poly (D,L,-lactide-co-glycoside) (80 mg zeranol; 4 pellets of 20 mg each) [98 mg total zeranol]

H Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release /poly (D,L-lactide-co-glycolide) (160 mg zeranol; 8 pellets of 20 mg zeranol each) [178 mg total zeranol]

I Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release /ethyl cellulose (160 mg zeranol; 8 pellets of 20 mg zeranol each) [178 mg total zeranol]

J Zeranol immediate-release (1 pellet of 18 mg zeranol) + Zeranol controlled-release /ethyl cellulose (80 mg zeranol; 4 pellets of 20 mg zeranol each) [98 mg zeranol total]

As can be seen, to prepare the inventive dual formulations H and I, one zeranol immediate-release pellet and 8 zeranol controlled-release pellets were taken in the device. Similarly, to prepare the inventive dual formulations G and J containing just half the amount of the controlled-release formulation, one zeranol immediate-release pellet and 4 controlled-release pellets were taken in the device. The immediate-release pellets and control release pellets were formulated as in Example 1 and administered to six groups of cattle in a similar fashion, i.e., subcutaneously under the ear. Again, in order to compare the improved formulations with the prescriptions currently followed in the veterinary art,

formulation F was administered twice, once (36 mg) at day 0 and again (36 mg) at day 70. Each steer was weighed at different intervals during its development and the average weight for each group given a particular formulation was averaged for each date. The formulations and average weight gain results for each are as follows:

Table 2

Treatment Formulation	Average Body Weight (in kilograms) Day (-1)	Day 0	Day 28	Day 56	Day 84	Day 112	Day 140
E	309	303	352	389	425	461	491
F	309	300	356	398	435	477	511
G	308	301	354	401	444	485	525
H	309	302	358	404	445	485	525
I	309	302	357	408	451	494	533
J	309	302	356	402	443	481	518

As is evidenced by the results shown for formulations G-J, superior growth and weight gains were observed with the inventive dual release formulations. Thus, when one (out of nine) of the controlled-release formulation pellets was replaced with one immediate-release pellet (formulations H and I), the weight gain became significantly higher than the results observed following the standard immediate re-implant program (formulation F) above. Such improvement was also noticed even when the controlled-release fraction was reduced by half (from 160 to 80 mg or 8 to 4 pellets) as shown in formulations G and J.

CLAIMS

What is claimed is:

1. An anabolic implant composition for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle, said composition comprising: (i) an immediate-release formulation comprising an anabolic agent, and (ii) a controlled-release formulation comprising an anabolic agent and a controlled-release agent, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect said stimulation.

2. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation are present respectively in a weight ratio range 1:2 to 1:25 in said composition.

3. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation are present respectively in a weight ratio range 1:2 to 1:10 in said composition.

4. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation are present respectively in a weight ratio range 1:3 to 1:8 in said composition.

5. The implant composition of claim 1, wherein said composition is subcutaneously injectable in said cattle.

6. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation contain the same anabolic agent.

7. The implant composition of claim 1, wherein said immediate-release formulation and said controlled-release formulation contain different anabolic agents.

8. The implant composition of claim 1, wherein said anabolic agent is selected from the group consisting of zeranol, estradiol, estradiol benzoate, trenbolone, trenbolone acetate, somatotrophin, testosterone, testosterone propionate, salbutamol, progesterone, and combinations, salts and derivatives thereof.

9. The implant composition of claim 8, wherein said anabolic agent is zeranol.

10. The implant composition of claim 8, wherein said anabolic agent is trenbolone acetate.

11. The implant composition of claim 9, wherein said zeranol is the anabolic agent in both said immediate-release formulation and said controlled-release formulation and comprises from about 50 wt.% to about 95 wt.% of said composition based on a total weight percentage basis.

12. The implant composition of claim 9, wherein said zeranol is the anabolic agent in both said immediate-release formulation and said controlled-release formulation and comprises from about 60 wt.% to about 80 wt % of said composition.

13. The implant composition of claim 1, wherein said immediate-release formulation additionally contains a diluent.

14. The implant composition of claim 13, wherein said diluent is selected from the group consisting of lactose, mannitol, sorbitol, sucrose, dextrose, starches, hydrolyzed starches, and combinations thereof.

15. The implant composition of claim 14, wherein said diluent is lactose.

16. The implant composition of claim 1, wherein said controlled-release agent is selected from the group consisting of poly(D,L-lactide-co-glycolide), ethyl cellulose, methyl acrylate-methyl methacrylate copolymer, methyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and combinations thereof.

17. The implant composition of claim 16, wherein said controlled-release agent is poly(D,L-lactide-co-glycolide).

18. The implant composition of claim 16, wherein said controlled-release agent is ethyl cellulose.

19. The implant composition of claim 1, wherein said controlled-release agent comprises from about 1.0 wt.% to about 8.0 wt.% based on the total weight of said implant composition.

20. The implant composition of claim 1, further comprising a bulking agent, binder, excipient, tabletting agent, colorant and combinations thereof.

21. A method for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in cattle, comprising the administration of an anabolic implant composition to said cattle which composition

comprises: (i) an immediate-release formulation comprising an anabolic agent, and (ii) a controlled-release formulation comprising an anabolic agent and a controlled-release agent, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect said stimulation.

22. The method of claim 21, wherein said immediate-release formulation and said controlled-release formulation are present in a weight ratio 1:25 in said composition.

23. The method of claim 21, wherein said administration comprises subcutaneously injecting said composition into said cattle.

24. The method of claim 21, wherein said immediate-release formulation and said controlled-release formulation contain the same anabolic agent.

25. The method of claim 21, wherein said immediate-release formulation and said controlled-release formulation contain different anabolic agents.

26. The method of claim 21, wherein said anabolic agent is selected from the group consisting of zeranol, estradiol, estradiol benzoate, trenbolone, trenbolone acetate, somatotrophin, testosterone, testosterone propionate, salbutamol, progesterone, and combinations, salts and derivatives thereof.

27. The method of claim 26, wherein said anabolic agent is zeranol.

28. The method of claim 27, wherein said zeranol is the anabolic agent in both said immediate-release formulation and said controlled-release formulation and comprises from about 50 wt.% to about 95 wt.% of said composition.

29. The method of claim 27, wherein zeranol is the anabolic agent in both said immediate-release formulation and said controlled-release formulation and comprises from about 60 wt.% to about 80 wt % of said composition.

30. The method of claim 21, wherein said immediate-release formulation additionally contains a diluent.

31. The method of claim 30, wherein said diluent is selected from the group consisting of lactose, mannitol, sorbitol, sucrose, dextrose, starches, hydrolyzed starches, and combinations thereof.

32. The method of claim 31, wherein said diluent is lactose.

33. The method of claim 21, wherein said controlled-release agent is selected from the group consisting of poly(D,L-lactide-co-glycolide), ethyl cellulose, methyl acrylate-methyl methacrylate copolymer, methyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and combinations thereof.

34. The method of claim 33 , wherein said controlled-release agent is poly(D,L-lactide-co-glycolide).

35. The method of claim 33, wherein said controlled-release agent is ethyl cellulose.

36. The method of claim 21, further comprising a bulking agent, binder, tabletting agent, excipient, colorant and combinations thereof.

37. A method for stimulating increased rate of growth, greater amount of growth and greater feed efficiency in an animal, said process comprising:

(a) preparing an immediate-release formulation comprising an anabolic agent, in a first shaped object suitable for loading into a device which device is suitable for administration of said shaped object into the animal;

(b) preparing a controlled-release formulation comprising an anabolic agent and a controlled-release agent, in a second shaped object suitable for loading into said device in step (a), wherein said anabolic agent in step (a) and said anabolic agent in step (b) may be the same or different,

(c) loading said device with said first shaped object and said second shaped object in a ratio such that the total anabolic agent is in the 50-95 weight percent range based on the combined weight of said formulation in step (a) and said formulation in step (b); and

(d) administering said shaped objects into the animal, wherein said immediate-release formulation and said controlled-release formulation cooperate to effect the stimulation.

38. The method of claim 37, wherein said anabolic agent in step 9a) and step (b) is the same and is zeranol.

39. The method of claim 37, wherein said controlled-release agent in step (b) is poly(D,L-lactide-co-glycolide), ethyl cellulose, methyl acrylate-methyl methacrylate copolymer, methyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and combinations thereof.

40. The method of claim 37, further containing lactose in step (a), step (b) or both.

41. The method of claim 37, wherein said first shaped object, or said second shaped object, or both is a tablet.

42. The method of claim 37, wherein said first shaped object, said second shaped object, or both is a pellet.

ABSTRACT OF THE INVENTION

An improved weight and growth stimulant for domesticated animals such as cattle, pigs and sheep is comprised of an anabolic agent that is subcutaneously administered in the form of a dual release implant formulation. Increased gains are particularly improved when zeranol is administered in an immediate-release and controlled-release formulation which allows for a one-time dosage injection.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	AH0948Q
First Named Inventor	SHIH, et al
COMPLETE IF KNOWN	
Application Number	/
Filing Date	November 2, 1999
Group Art Unit	TO BE ADVISED
Examiner Name	TO BE ADVISED

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

(Title of the Invention)

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) _____ as United States Application Number or PCT International Application Number _____ and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
60/107,056	11/04/98

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: _____

Typed or printed name			
Signature		Date	

Express Mail Label No.	EL226882657US
Date	Nov. 2, 1999

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → Place Customer Number Bar Code Label here
OR
☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] OR ☒ Correspondence address below

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Address	2000 Galloping Hill Road				
City	Kenilworth	State	NJ	ZIP	07033-0530
Country	USA	Telephone	(908) 298-5037	Fax	(908) 298-5388

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
CHUNG	SHIH

Inventor's Signature						Date	
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☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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Supplemental Sheet
Page 1 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
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Inventor's Signature						**Date**	
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Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
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Inventor's Signature						**Date**	
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Post Office Address							
City	Warren	**State** NJ	**ZIP** 08886		**Country** U.S.A.		

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
DANIEL S.			ROBINS				
Inventor's Signature	Daniel S. R					**Date**	10/18/99
Residence: City	New York	**State** NY		**Country** U.S.A.		**Citizenship**	U.S.A.
Post Office Address	77 E. 12th Street, Apt. 3B						
Post Office Address							
City	New York	**State** NY	**ZIP** 10003-5003		**Country** U.S.A.		

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ADDITIONAL INVENTOR(S)
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Page 2 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
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Inventor's Signature						**Date**	
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City	Basking Ridge	**State**	NJ	**ZIP**	07920	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname

Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
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City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname

Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

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REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

Name	Registration Number	Name	Registration Number
Carl W. Battle	30731	Gabriel P. Kralik	34855
Edwin P. Ching	34090	Susan Lee	30653
Eric S. Dicker	31669	Anita W. Magatti	29825
Cynthia L. Foulke	32364	Arthur Mann	35598
Robert A. Franks	28605	Edward H. Mazer	27573
Kenneth M. Goldman	34174	Jaye P. McLaughlin	41211
James M. Gould	33702	Richard B. Murphy	35296
Richard J. Grochala	31518	James R. Nelson	27929
Henry S. Hadad	35888	David B. Schram	43096
Thomas D. Hoffman	28221	Immac J. Thampoe	36322
Henry C. Jeanette	30856	Paul A. Thompson	35385
Palaiyur S. Kalyanaraman	34634	Joanne P. Will	35737
Gerald P. Keleher	43707	Donald W. Wyatt	40879

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	AH0948Q
First Named Inventor	SHIH, et al
COMPLETE IF KNOWN	
Application Number	/
Filing Date	November 2, 1999
Group Art Unit	TO BE ADVISED
Examiner Name	TO BE ADVISED

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

(Title of the Invention)

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) [ ] as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

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60/107,056	11/04/98

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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Signature		Date	

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U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*

OR

☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] *OR* ☒ Correspondence address below

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
CHUNG	SHIH

Inventor's Signature						Date	
Residence: City	Sandy	State	UT	Country	U.S.A.	Citizenship	U.S.A.
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City	Sandy	State	UT	ZIP	84093	Country	U.S.A.

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

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Given Name (first and middle [if any])				Family Name or Surname			
THOMAS J.				KENNEDY			
Inventor's Signature						**Date**	
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Post Office Address							
City	Waunakee	**State**	WI	**ZIP**	53597	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
PETER JAMES				KNIGHT			
Inventor's Signature						**Date**	
Residence: City	Stewartsville	**State**	NJ	**Country**	U.SA..	**Citizenship**	UK
Post Office Address	1826 Gary Road						
Post Office Address							
City	Warren	**State**	NJ	**ZIP**	08886	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
DANIEL S.				ROBINS			
Inventor's Signature						**Date**	
Residence: City	New York	**State**	NY	**Country**	U.S.A.	**Citizenship**	U.S.A.
Post Office Address	77 E. 12th Street, Apt. 3B						
Post Office Address							
City	New York	**State**	NY	**ZIP**	10003-5003	**Country**	U.S.A.

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 2 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
ZEZHI, JESSE			SHAO				
Inventor's Signature						**Date**	10/18/99
Residence: City	BASKING RIDGE	**State** NJ		**Country** U.S.A.		**Citizenship**	U.S.A.
Post Office Address	68 Patriot Hill Drive						
Post Office Address							
City	Basking Ridge	**State** NJ	**ZIP** 07920		**Country** U.S.A.		

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

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DECLARATION

REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

Name	Registration Number	Name	Registration Number
Carl W. Battle	30731	Gabriel P. Kralik	34855
Edwin P. Ching	34090	Susan Lee	30653
Eric S. Dicker	31669	Anita W. Magatti	29825
Cynthia L. Foulke	32364	Arthur Mann	35598
Robert A. Franks	28605	Edward H. Mazer	27573
Kenneth M. Goldman	34174	Jaye P. McLaughlin	41211
James M. Gould	33702	Richard B. Murphy	35296
Richard J. Grochala	31518	James R. Nelson	27929
Henry S. Hadad	35888	David B. Schram	43096
Thomas D. Hoffman	28221	Immac J. Thampoe	36322
Henry C. Jeanette	30856	Paul A. Thompson	35385
Palaiyur S. Kalyanaraman	34634	Joanne P. Will	35737
Gerald P. Keleher	43707	Donald W. Wyatt	40879

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	AH0948Q
First Named Inventor	SHIH, et al
COMPLETE IF KNOWN	
Application Number	/
Filing Date	November 2, 1999
Group Art Unit	TO BE ADVISED
Examiner Name	TO BE ADVISED

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

(Title of the Invention)

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) [ ] as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/107,056	11/04/98	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: [ ]

Typed or printed name			
Signature		Date	

Express Mail Label No.	EL226882657US
Date	Nov. 2, 1999

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*

OR

☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] *OR* ☒ Correspondence address below

Name	PALAIYUR S. KALYANARAMAN				
Address	Patent Dept. K-6-1, 1990	Schering-Plough Corporation			
Address	2000 Galloping Hill Road				
City	Kenilworth	**State**	NJ	**ZIP**	07033-0530
Country	USA	**Telephone**	(908) 298-5037	**Fax**	(908) 298-5388

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
CHUNG	SHIH

Inventor's Signature	Chung Shih					**Date**	04/9/99
Residence: City	Sandy	**State**	UT	**Country**	U.S.A.	**Citizenship**	U.S.A.
Post Office Address	2798 E. Amberwick Lane						
Post Office Address							
City	Sandy	**State**	UT	**ZIP**	84093	**Country**	U.S.A.

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
THOMAS J.				KENNEDY			
Inventor's Signature						**Date**	
Residence: City	WAUNAKEE	**State**	WI	**Country**	U.S.A.	**Citizenship**	U.S.A.
Post Office Address	5492 Kennedy Drive						
Post Office Address							
City	Waunakee	**State**	WI	**ZIP**	53597	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
PETER JAMES				KNIGHT			
Inventor's Signature						**Date**	
Residence: City	Stewartsville	**State**	NJ	**Country**	U.SA..	**Citizenship**	UK
Post Office Address	1826 Gary Road						
Post Office Address							
City	Warren	**State**	NJ	**ZIP**	08886	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
DANIEL S.				ROBINS			
Inventor's Signature						**Date**	
Residence: City	New York	**State**	NY	**Country**	U.S.A.	**Citizenship**	U.S.A.
Post Office Address	77 E. 12th Street, Apt. 3B						
Post Office Address							
City	New York	**State**	NY	**ZIP**	10003-5003	**Country**	U.S.A.

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ZEZHI, JESSE	SHAO

Inventor's Signature						**Date**	
Residence: City	BASKING RIDGE	**State**	NJ	**Country**	U.S.A.	**Citizenship**	U.S.A.
Post Office Address	68 Patriot Hill Drive						
Post Office Address							
City	Basking Ridge	**State**	NJ	**ZIP**	07920	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname

Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

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Given Name (first and middle [if any])	Family Name or Surname

Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

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Robert A. Franks	28605	Edward H. Mazer	27573
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James M. Gould	33702	Richard B. Murphy	35296
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Henry C. Jeanette	30856	Paul A. Thompson	35385
Palaiyur S. Kalyanaraman	34634	Joanne P. Will	35737
Gerald P. Keleher	43707	Donald W. Wyatt	40879

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	AH0948Q
First Named Inventor	SHIH, et al
COMPLETE IF KNOWN	
Application Number	/
Filing Date	November 3, 1999
Group Art Unit	TO BE ADVISED
Examiner Name	TO BE ADVISED

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

(Title of the Invention)

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) _____ as United States Application Number or PCT International Application Number _____ and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/107,056	11/04/98	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

CERTIFICATE OF MAILING

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Typed or printed name			
Signature		Date	

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Date	11/2/99

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U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → Place Customer Number Bar Code Label here

OR

☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] OR ☒ Correspondence address below

Name	PALAIYUR S. KALYANARAMAN				
Address	Patent Dept. K-6-1, 1990	Schering-Plough Corporation			
Address	2000 Galloping Hill Road				
City	Kenilworth	State	NJ	ZIP	07033-0530
Country	USA	Telephone	(908) 298-5037	Fax	(908) 298-5388

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
CHUNG	SHIH

Inventor's Signature						Date	
Residence: City	Sandy	State	UT	Country	U.S.A.	Citizenship	U.S.A.
Post Office Address	2798 E. Amberwick Lane						
Post Office Address							
City	Sandy	State	UT	ZIP	84093	Country	U.S.A.

☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
THOMAS J.	KENNEDY

Inventor's Signature						**Date**	29 Oct 99
Residence: City	WAUNAKEE	**State**	WI	**Country**	U.S.A.	**Citizenship**	U.S.A.
Post Office Address	5492 Kennedy Drive						
Post Office Address							
City	Waunakee	**State**	WI	**ZIP**	53597	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
PETER JAMES	KNIGHT

Inventor's Signature						**Date**	
Residence: City	Stewartsville	**State**	NJ	**Country**	U.SA..	**Citizenship**	UK
Post Office Address	1826 Gary Road						
Post Office Address							
City	Warren	**State**	NJ	**ZIP**	08886	**Country**	U.S.A.

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
DANIEL S.	ROBINS

Inventor's Signature						**Date**	
Residence: City	New York	**State**	NY	**Country**	U.S.A.	**Citizenship**	U.S.A.
Post Office Address	77 E. 12th Street, Apt. 3B						
Post Office Address							
City	New York	**State**	NY	**ZIP**	10003-5003	**Country**	U.S.A.

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ZEZHI, JESSE			SHAO				
Inventor's Signature						**Date**	
Residence: City	BASKING RIDGE	**State** NJ		**Country** U.S.A.		**Citizenship**	U.S.A.
Post Office Address	68 Patriot Hill Drive						
Post Office Address							
City	Basking Ridge	**State** NJ	**ZIP** 07920	**Country** U.S.A.			

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Given Name (first and middle [if any])			Family Name or Surname				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**	**ZIP**	**Country**			

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Given Name (first and middle [if any])			Family Name or Surname				
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**	**ZIP**	**Country**			

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Cynthia L. Foulke	32364	Arthur Mann	35598
Robert A. Franks	28605	Edward H. Mazer	27573
Kenneth M. Goldman	34174	Jaye P. McLaughlin	41211
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	AH0948Q
First Named Inventor	SHIH, et al
COMPLETE IF KNOWN	
Application Number	/
Filing Date	November 2, 1999
Group Art Unit	TO BE ADVISED
Examiner Name	TO BE ADVISED

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED GROWTH STIMULANT COMPOSITIONS

(Title of the Invention)

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) [ ] as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/107,056	11/04/98	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date:

Typed or printed name			
Signature		Date	

Express Mail Label No.	EL226882657US
Date	Nov. 2, 1999

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (12-97)
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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → Place Customer Number Bar Code Label here
OR
☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number

☒ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] OR ☒ Correspondence address below

Name	PALAIYUR S. KALYANARAMAN				
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
CHUNG	SHIH

Inventor's Signature						Date	
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☒ Additional inventors are being named on the 2 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → [+]

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ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])			Family Name or Surname				
THOMAS J.			KENNEDY				
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Given Name (first and middle [if any])			Family Name or Surname				
PETER JAMES			KNIGHT				
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City	New York	**State** NY	**ZIP** 10003-5003	**Country** U.S.A.			

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 2 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
ZEZHI, JESSE				SHAO			
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Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
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Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
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City		**State**		**ZIP**		**Country**	

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])				Family Name or Surname			
Inventor's Signature						**Date**	
Residence: City		**State**		**Country**		**Citizenship**	
Post Office Address							
Post Office Address							
City		**State**		**ZIP**		**Country**	

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DECLARATION

REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

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